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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,750	02/19/2004	Joseph P. Vacanti	MIT 6917 (CMCC 450) DIV	5014

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PATREA L. PABST
PABST PATENT GROUP LLP
400 COLONY SQUARE
SUITE 1200
ATLANTA, GA 30361

EXAMINER	
ISABELLA, DAVID J	

ART UNIT	PAPER NUMBER
3738	

DATE MAILED: 06/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,750	VACANTI ET AL.	
	Examiner	Art Unit	
	DAVID J. ISABELLA	3738	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of the Application

A final rejection was mailed on 4/10/2006 and applicant response to the final dated 3/13/2006 was considered. An advisory action was mailed on 3/29/2006 detailing the status of the newly presented claims 16 and 17 and the outstanding rejection to the claims.

With respect to the restriction, examiner withdrew newly added claims 16 and 17 as being directed to subject matter not originally presented. Examiner statement of the advisory is presented below.

Applicant's argues that there can be no use of the cell matrix other than with the claimed method. The language of "for use as a head valve or head valve:" does not exclude the construct to be used in other methods. The language is and intended use but does not exclude or prohibit the construct to be used for other applications. The claim as worded is broadly directed to a cell-matrix construct comprising a fibrous polymeric matrix having a shape; the matirx is formed of biodegradable polymer having seeded cells thereon. Moreover, the construct requires the myofibroblasts be cultured to confluence and then endothelial cells are seeded on the confluent matrix. The method does not require the respective steps for seeding the cells and the method for making the construct must take place in vivo whereas the construct of claims 16 and 17 do not have such requirement. As outlined in the last Office action, the newly submitted claims 16 and 17 are directed to an invention that is independent or distinct from the invention originally claimed because the newly added claims are directed to a "cell matrix construct" seeded with myofibroblasts. The original claims were directed to a method for making a cell matrix construct including implanting a construct into an animal. The construct of claims 16-17 does not require it to be specific to vivo ' harvesting and therefor is directed to subject matter not originally considered.

Accordingly, claims 16 and 17 remain withdrawn from consideration as being drawn to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

In accordance with MPEP section 1451, applicant may elected to file a divisional application for each inventions identified in the restriction by the examiner.

> 37 CFR 1.176(b) permits the examiner to require restriction in a reissue application between the original claims of the patent and any newly added claims which are directed to a separate and distinct invention(s). See also MPEP § 1450. As a result of such a restriction requirement, divisional applications may be filed for each of the inventions identified in the restriction requirement.

With respect to the rejection to the claimed invention, examiner's advisory action included a summary of the applied references and their combination.

. Examiner summary of the rejection in the advisory is presented below.

Applicant argues that the prior ad must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. Applicant attempt to remove Sparks as a base reference is not convincing. Applicant argues that the implant of Sparks includes structures such as an outer die member, inner die member screws, ring and no way can these metal structures be compared to a fibrous mesh. Applicant further argues that the claim requires the construct be formed entirely of a mesh. Examiner respectfully disagrees with applicant's interpretation of Sparks and Claim 1. With respect to Sparks, Dacron mesh is utilized as the fabric (ie. fibrous matrix) upon which cells are seeded. The various metal structures are utilized as support or framework to support mesh in the proper configuration. With respect to the requirement that the construct be formed entirely of a mesh, examiner contends that claim 1, as broadly worded, does not preclude the use: of additional structure, including supporting or framework for supporting the fibrous matrix in keeping with proper analogy between the claimed invention and the construct of Sparks, one with ordinary skill in the ad would equate the fibrous matrix of the claim to be equivalent in structure and function to the Dacron mesh of Sparks. As argued by the examiner, Sparks clearly discloses a method for making a cell-matrix construct for use as a heart valve comprising implanting into an animal a fibrous matrix formed of a polymer that has been seeded with specific selected cells. Contrary to applicant's arguments that Sparks fails to disclose a method for making a shaped construct in the likeness of a heart valve,

examiner directs applicant's attention to column 5,lines 5-75. In column 5, Sparks specifically discloses the method for forming any of a tricuspid, bicuspid or individual valve leaflets. Clearly, the resulting construct of Sparks is in the form of a heart valve as broadly claimed by applicant. . It should be evident that at the time of Sparks invention (1967) the use of resorbable material in tissue applications was in its infancy. At the time of applicant's invention (2004), great strides have been made in the prosthetic art in replacing non-resorbable materials with resorbable materials for various known benefits. The use of resorbable material as the substrate for seeding cells to form a tissue construct would have been obvious to one with ordinary skill in the art from the teachings of any of the secondary references. ; ! Examiner argued that Applicant specification is silent any unobvious benefits in the selection of the materials used for the seeding of the cells. Accordingly, examiner l maintains that the materials used by applicant are well known in the ad and are in many instances, known equivalents as taught by Jauregui or Tang et al. Specifically, Tang, et al teaches that bioabsorbable material play critical role in fabrication of devices used for tissue regeneration.

Response to Applicant's Request

The finality of the final Office Action has been withdrawn. Examiner has rewritten the final action to better clarify the outstanding rejection to the claims and the status of the non-elected claims. The instant Office action is made final as no new arguments or prior art has been presented.

Status of the Claims

Claims 1-5,8-17 are currently pending for action. Claims 6 and 7 have been cancelled. Claims 16 and 17 have been newly added. Claims 1,2,15 have been amended.

Election/Restrictions

Newly submitted claims 16 and 17 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims are directed to a cell matrix construct seeded with myofibroblasts. The original claims were directed to a method for making a cell matrix construct including implanting the construct into an animal. The construct of claims 16-17 does not require the specific in vivo harvesting of the construct and therefor is directed to subject matter not originally considered.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 16 and 17 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5,8-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sparks (3514791) in view of Mikos (5514378) or Griffith-Cima et al (5709854) and in view of the teachings of either of Jauregui (4795459) or Tang et al (4916193).

Sparks discloses a method for making a cell-matrix construct for use as a heart valve comprising implanting into an animal a fibrous matrix formed of a polymer that has been seeded

with specific selected cells. See column 5,lines 5-75 for specific disclosure directed to the method for forming any of a tricuspid, bicuspid or individual valve leaflets.

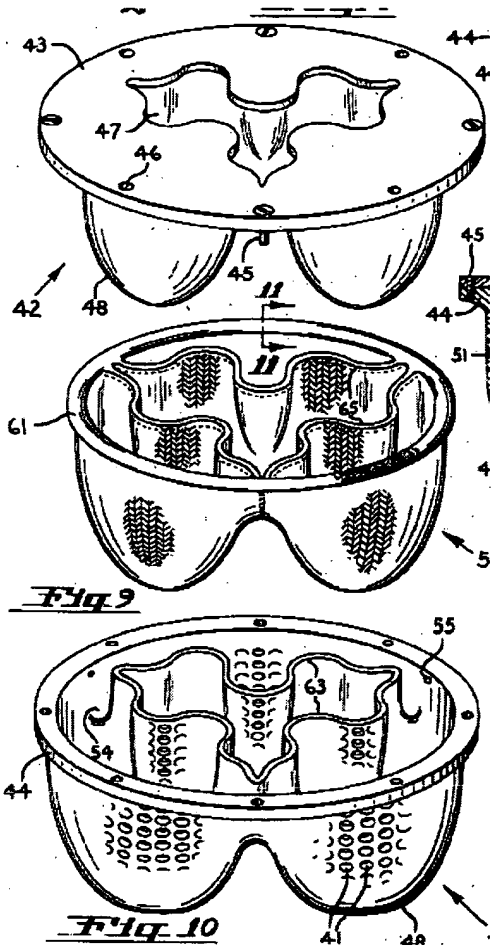

Fig 9

Fig 10

Sparks fails to teach that the matrix is biodegradable. Mikos and Griffith-Cima et al teach the use of biodegradable matrix which is designed to allow biological tissue ingrowth to form a structure before the matrix is completely bioabsorbed.

Mikos, column 2, lines 15+, discloses an article by Vacanti, et al (1988) teaching that the scaffold should mimic the natural tissue counterpart. Moreover, Vacanti, et al provides evidence that better results are obtained when the matrix is first implanted, prevascularized and then seeded with select cells.

> Vacanti, et al., "Selective cell transplantation using bioabsorbable artificial polymers as matrices" *J. Pediat. Surg.* 23, 3–9 (1988) and Vacanti, "Beyond Transplantation" *Arch. Surg.* 123, 545–549 (1988), describe an approach for making new organs for transplantation which was not subject to the same limitations as the work of Yannas and Burke, i.e., it was not limited to the construction of very thin organs such as skin. Vacanti, et al., recognized that cells require a matrix for attachment and support if they are to survive following implantation, that a minimum number of cells was essential for function in vivo, and that the matrix must be porous enough to allow nutrients and gases to reach all of the cells on and within the matrix by diffusion, until the matrix-cell structure was vascularized. Moreover, they recognized the advantage of using synthetic biodegradable polymer substrates to form a scaffold that mimics its natural counterparts, the extracellular matrices (ECM) of the body, serving as both a physical support and an adhesive substrate for isolated parenchymal cells during in vitro culture, and subsequent implantation, degrading as the cells begin to secrete they own ECM support. Subsequent studies have demonstrated that even better results are obtained when the matrix is first implanted, prevascularized, and then seeded with cells. Most matrices used in the earlier work are modifications of materials already available, such as surgical sutures and meshes. This latter approach, however, requires new matrix configurations which are optimal for vascularization, yet resistant to compression, with sufficient porosity and interconnected interstitial spacings to allow injected cells to become dispersed throughout the matrix.

Furthermore, Mikos is specific as to the purpose of tailoring the bioabsorbable matrix according to the selected biological tissue to be grown. See column 13, lines 31+.

> The matrix scaffold is used to mimic its natural counterparts, the extracellular matrices (ECM) of the body. It serves as both a physical support and an adhesive substrate for isolated parenchymal cells during in vitro culture and subsequent implantation. As the transplanted cell population grows and the cells function normally, they begin to secrete their own ECM support. Concurrently, when using a biodegradable matrix material, the scaffold continuously degrades and is eliminated as the need for an artificial support diminishes. In the reconstruction of structural tissues like cartilage and bone, tissue shape is integral to function. Therefore, these scaffolds must be processable into devices of varying thickness and shape.
>
> Preparation of Anatomical Shapes
>
> The membranes are processed into anatomical shapes, or foams, for use in reconstructive surgery or organ transplantation, as depicted in FIG. 3 (described in more detail

Moreover, Mikos teaches that various cells types may be used for culturing new tissues. See column 14, lines 25+.

Use of the Matrix for Reconstructive Surgery

The three-dimensional structure is specifically designed to provide a matrix for dissociated cells such as chondrocytes or hepatocytes to create a three-dimensional tissue or organ. Any type of cell can be added to the matrix for culturing and possible implantation, including cells of the muscular and skeletal systems, such as chondrocytes, fibroblasts, muscle cells and osteocytes, parenchymal cells such as hepatocytes, pancreatic cells (including Islet cells), cells of intestinal origin, and other cells such as nerve cells and skin cells, either as obtained from donors, from established cell culture lines, or even before or after genetic engineering. Pieces of tissue can also be used, which may provide a number of different cells types in the same structure.

The cells are obtained from a suitable donor or the patient into which they are to be implanted, dissociated using standard techniques, and seeded onto and into the matrix. These are optionally cultured in vitro prior to implantation. Alternatively, the matrix is implanted, allowed to vascularize, then the cells injected into the matrix. Methods and reagents for culturing cells in vitro and implantation of a matrix are known to those skilled in the art.

Griffith-Cima teaches that the degradable template may be shaped or formed prior to implantation into the patient.

the hydrogel. However, the matrix may also be molded and implanted in one or more different areas of the body to suit a particular application. This application is particularly relevant where a specific structural design is desired or where the area into which the cells are to be implanted lacks specific structure or support to facilitate growth and proliferation of the cells.

The site, or sites, where cells are to be implanted is determined based on individual need, as is the requisite number of cells. For cells having organ function, for example, hepatocytes or islet cells, the mixture can be injected into the mesentery, subcutaneous tissue, retroperitoneum, properitoneal space, and intramuscular space. For formation of cartilage, the cells are injected into the site where cartilage formation is desired. One could also apply an external mold to shape the injected solution. Additionally, by controlling the rate of polymerization, it is possible to mold the cell-hydrogel injected implant like one would mold clay.

Alternatively, the mixture can be injected into a mold, the hydrogel allowed to harden, then the material implanted.

Each of Jauregui and Tang et al teaches the doctrine of equivalence between resorbable and non resorbable materials as used in heart valve applications similar to that as disclosed in column 4 of applicants specification. To replace the non-absorbable mesh of Sparks with an absorbable matrix as taught by Mikos or Griffith-Cima et al to allow for a degradable template

for new tissue formation would have been obvious to one with ordinary skill in the art especially in light of the Vacanti publication (as disclosed in Mikos) which teaches the benefits of selected cells transplantation on bioabsorbable polymer matrix.

Applicant specification fails to teach and/or disclose any unobvious benefits or criticalities in the selection of the materials used for the seeding of the cells. Accordingly, examiner maintains that the materials used are well known in the art and are, in many instances, known equivalents as taught by Jauregui or Tang et al. It should be evident that at the time of Sparks invention (1967) the use of resorbable material in tissue applications was in its infancy. At the time of applicant's invention (2004), great strides have been made in the prosthetic art in replacing non-resorbable materials with resorbable materials for various known benefits. The use of resorbable material as the substrate for seeding cells to form a tissue construct would have been obvious to one with ordinary skill in the art from the teachings of any of the secondary references. With respect to the limitation of "withstand repeated stress and strain", the device of Sparks as modified would inherently possess the properties that would be capable of withstanding cyclic stresses and strains since the valve is designed to function as a replacement of a natural existing valve.

Claim 2, see cells disclosed by Sparks.

Claim 3, Sparks discloses the steps of culturing a matrix at a first site then transplanting the new tissue to a desired site.

Claim 4, one embodiment disclosed by Sparks is a heart valve.

Claim 5, see cells of sparks or Schmidt, et al.

Claim 8, the newly formed heart tissue of Sparks would inherently possess the strength, flexibility and/or pliability of the tissue it is to replace.

Claims 9 and 10, see materials disclosed by Mikos or Griffith-Cima et al.

Claim 11, see Mikos.

Claims 12-14, see Mikos or Griffith-Cima et al.

Claim 15, see construct of Sparks as modified by either of Mikos or Griffith-Cima et al.

Response to Arguments

Applicant's arguments filed 3/13/2006 have been fully considered but they are not persuasive.

Applicant argues that Sparks does not teach or suggest that the polymer matrix is seeded with cells. But rather that Sparks relies on natural body processes to produce the necessary connective tissue to the die cavity and form the valve. While it is not entirely clear if Sparks supports applicant's interpretation, examiner maintains Sparks discloses various methods for populating and growing new tissues including seeding, preclotting the matrix with blood and natural induction of tissue growth into the matrix. Beyond Sparks, it was certainly known at the time of applicant's invention to preseed polymer matrix prior to implanting the matrix in the body for growing new tissue. Applicant's attention is directed to Mikos specification, in the background of the invention, Vacanti's teachings for preseeding polymer matrixes prior to implantation to optimize new tissue formation and growth.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID J. ISABELLA whose telephone number is 703-308-3060. The examiner can normally be reached on MONDAY-THURSDAY.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, CORRINE MCDERMOTT can be reached on 571-272-4754. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVID J ISABELLA
Primary Examiner
Art Unit 3738

DJI
5/25/2006